Seeing what you want to see in randomized controlled trials: versions and perversions of UK Prospective Diabetes Study data

INTRODUCTION

Randomized controlled trials are objective, free of bias, and produce robust conclusions about the benefits and risks of treatment, and clinicians should be trained to rely on them—so says the gospel of evidence-based practice. In this article we argue, using the United Kingdom Prospective Diabetes Study (UKPDS) as an example, that 1 of the stages in the conduct of a randomized controlled trial—the interpretation and dissemination of results—is open to several biases that can seriously distort the conclusions. By bias, we mean the epidemiologic definition: anything that systematically distorts the comparisons between groups. We argue that certain biases arise when different stakeholders assign their individual values to the interpretation of the final results of randomized controlled trials.

Summary points

- Randomized trials are subject to interpretation bias, as shown by the example of the UK Prospective Diabetes Study
- This study shows no benefit on macrovascular end points in patients with type 2 diabetes treated with sulfonylureas or insulin over 10 years
- The study shows a clinically important benefit on macrovascular end points from the use of metformin in patients with type 2 diabetes that seems independent of the drug's ability to lower blood glucose concentrations
- Nevertheless, many authors, journal editors, and the wider scientific community interpreted the study as providing evidence of the benefit of intensive glucose control
- Journal editors should be aware of this important potential bias and encourage authors to present their results initially with a minimum of discussion so as to invite a range of comments and perspectives from readers

MARKETING THE UKPDS RESULTS

Until 1998, type 2 diabetes had been treated for more than 25 years with drugs such as the sulfonylureas, insulin, and metformin. Only 1 well-designed, prospective clinical trial had evaluated the effect of these drugs on the development of microvascular and macrovascular disease. This was the University Group Diabetes Program study, the results of which created considerable controversy because the researchers showed an increased risk of death from cardiovascular disease in the group receiving sulfonylureas.[1] Perhaps because of this controversy, the results had little effect. The fact that the trial was never repeated and that no further randomized controlled trials were published for another 25 years may surprise many clinicians. In September 1998, the long-awaited results from the

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Table 1 *Effect of 10 years' treatment with chlorpropamide, glibenclamide, or insulin on patients (2,505 nonobese and 1,362 obese) with newly diagnosed type 2 diabetes*

Treatment	Any diabetes-related end points, %*	Microvascular disease, %	Individual macrovascular disease end points†	Median hemoglobin A_{1c} concentration, %
Dietary advice plus chlorpropamide, glibenclamide, or insulin	35.3	8.2	No significant difference between the groups for any of the end points‡	Chloropropamide, 6.7; glibenclamide, 7.2; insulin, 7.1
Dietary advice only	38.5	10.6		7.9
Relative risk reduction	8.2	22.6		§
Absolute risk reduction	3.2‖	2.4		§
No. needed to treat for 10 yr to prevent 1 event	31	42		NA

NA = not applicable.
*Sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal myocardial infarction, angina, heart failure, stroke, renal failure, amputation, vitreous hemorrhage, retinal photocoagulation, blindness in 1 eye, or cataract extraction.
†Deaths related to diabetes, all-cause mortality, myocardial infarction, stroke, blindness, renal failure, or neurologic events.
‡The *P* value for myocardial infarctions was 0.05 (dietary advice plus drug treatment, 14.2%, vs dietary advice, 16.3%). However, because the study was continued after the initial results showed no differences, a breakpoint for significance of 0.05 is debatable.
§Significantly lower with all drugs compared with dietary advice.
‖Of this percentage, 2.7% was due to a significant reduction in the incidence of retinal photocoagulation.

UKPDS were presented in the *BMJ, Lancet,* and elsewhere.[2,3] The 20-year study was conducted in 23 centers in the United Kingdom. More than 5,000 patients with type 2 diabetes mellitus were recruited. The aim of the study was to determine the effect of intensive blood glucose control with the use of sulfonylureas, insulin, or metformin on 21 predetermined clinical end points.

Despite some of the methodologic limitations (the study was unblinded, the trial was continued when differences were not seen at the initial evaluation, and patients in the diet-only group received drug treatment if their fasting plasma glucose concentration was <15 mmol/L [<270 mg/dL]), the articles have some important messages for physicians and patients.[4,5] Indeed, no trials in the near future are likely to provide us with more information about the effect of glucose-lowering drug treatment on the microvascular and macrovascular complications of type 2 diabetes. In general, the reporting of the results of the trial was positive. Reviewers stated that:

- Clear and consistent evidence now exists that hyperglycemia in diabetes is a continuous, modifiable risk factor for clinically important outcomes and that reducing glucose concentrations is the key to improving outcomes[6]
- We now have convincing evidence that tight blood glucose control is an important goal for managing type 2 diabetes. Unless patients are seriously ill or have a short life expectancy, the long-term benefits of intensive therapy clearly outweigh the few risks[6]
- The main translatable finding is that intensive treatment of type 2 diabetes is beneficial[7]

Despite these widely disseminated conclusions, scrutiny of the published data seems to show that the sulfonylureas and insulin have no effect on clinically important outcomes.[2,3] In this article, we present the raw data and invite readers to draw their own conclusions and recommendations.

WHAT DID THE DATA SHOW?

Table 1 summarizes the 10-year results of the UKPDS 33,[2] which evaluated drug treatment in 2,505 nonobese and 1,362 obese participants with newly diagnosed type 2 diabetes who were referred to hospital clinics. We have expressed the data as percentages rather than events per 1,000 patient-years so that we can give absolute reductions and numbers needed to treat over a specific period. This allows comparison with the results of other trials that have been presented in this standardized way.[8] We realize that advantages and disadvantages exist and assumptions have to be made when presenting the results either way.[9]

The primary outcome for these trials was a reduction in the number of patients with an aggregate of clinical end points (table 1) or diabetes-related deaths. During the 10 years of the study, a 3.2% absolute reduction occurred in the occurrence of 1 of the aggregated end points developing. Most of this benefit was due to a 2.7% absolute reduction in the incidence of retinal photocoagulation, which was assessed by ophthalmologists independent of the study.

Closer evaluation of the results showed, however, that the use of glibenclamide (glyburide), chlorpropamide, or insulin to lower blood glucose concentrations produced no significant benefit on any single macrovascular end

point. A 2.4% absolute difference was seen for microvascular end points, and again, most of the benefit was due to the reduction in the incidence of retinal photocoagulation. Differences were detected in the surrogate end points of progression of retinopathy and albuminuria, but no differences were found in the prevalence of blindness, of visual acuity, or the incidence of renal failure.

Nevertheless, this trial has shown that the use of sulfonylureas probably does not increase the risk of death or serious disease events, which was a potential concern suggested by the results of the University Group Diabetes Program study.[1] It seems, therefore, that physicians can be confident in prescribing these drugs to control the symptoms of hyperglycemia in patients whose glucose concentrations are not adequately controlled by diet, exercise, and other oral drugs.

The UKPDS 33 suggests that the drugs used were well tolerated, although only hypoglycemic events and weight gain were reported. Nevertheless, participants in the sulfonylurea and insulin groups gained a mean of 3.1 kg (6.8 lb) more weight than the group treated with diet alone. Major hypoglycemic episodes (those requiring third-party help) occurred in 0.1%, 0.6%, 0.6%, and 2.3% of participants per year in the diet, chlorpropamide, glibenclamide, and insulin groups, respectively (note that benefit was expressed over 10 years). The incidence of minor hypoglycemic events was 1%, 11%, 18%, and 37% per year, respectively.

In contrast to the above-mentioned results, the UKPDS 34, which focused on 1,704 obese patients with newly diagnosed type 2 diabetes, found several clinically important differences in macrovascular disease end points with 10 years of treatment with metformin (table 2).[3] In particular, the absolute risk reduction for the aggregate end points was more than 10%, and for overall mortality was 7%, giving numbers needed to treat of 10 and 14, respectively, over 10 years. Furthermore, in these patients, the use of metformin was not associated with increased weight gain or hypoglycemic episodes compared with diet alone. Metformin reduced the progression of retinopathy compared with dietary advice alone, but no differences in other surrogate markers were found between the treatment groups.

Contrary to expectations, treatment with sulfonylureas and insulin had no significant benefit on the occurrence of microvascular or macrovascular end points over 10 years in this obese population (table 2). Metformin also produced significant reductions in the aggregated diabetes-related end points, all-cause mortality, and stroke compared with the sulfonylureas and insulin.

With regard to the results of these 2 trials, 1 message seems to have been lost from many of the commentaries on the UKPDS. That is, patients with type 2 diabetes seem to benefit not so much from the overall control of glucose but rather from taking metformin.

The study also raises an interesting point about hemoglobin A_{1c}, which to our knowledge has not been discussed in any detail. Hemoglobin A_{1c} concentration has been used for years as a surrogate marker. Although it is a good marker of overall blood glucose control, it is not

Table 2 *Effect of 10 years' treatment with metformin or chlorpropamide, glibenclamide, or insulin in overweight patients with newly diagnosed type 2 diabetes (N = 1,704)*

Treatment	Any diabetes related end points, %	Deaths related to diabetes, %	All-cause mortality, %	Myocardial infarction, %	Stroke, %	Microvascular disease, %	Median hemoglobin A_{1c} concentration, %
Dietary advice plus metformin	28.7*	8.2†	14.6*	11.4†	3.5‡	7.0	7.4
Dietary advice plus chlorpropamide, glibenclamide, or insulin	36.8	10.8	20.0	14.6	6.3	7.8	All similar to that with metformin
Dietary advice only	38.9	13.4	21.7	17.8	5.6	9.2	8.0
Relative risk reduction§	26.2	38.8	32.7	36.0	44.4‖	NS	¶
Absolute risk reduction§	10.2	5.2	7.1	6.4	2.8‖	NS	¶
No. needed to treat for 10 yr to prevent 1 event§	10	19	14	16	36‖	NS	¶

NS = not significant.
*Significant versus both other groups.
†Significant versus dietary advice
‡Significant versus chlorpropamide, glibenclamide, or insulin group.
§Metformin versus dietary advice.
‖These results are for the differences between the metformin group and the chlorpropamide, glibenclamide, or insulin group.
¶Significantly lower for all drugs compared with dietary advice.

known whether reducing hemoglobin A_{1c} concentrations in patients with type 2 diabetes leads to an improved outcome. To establish a causal relation between a surrogate marker and a clinical outcome, a dose-response relation must be shown—that is, that a consistent progressive clinical benefit is seen with progressive reductions in the surrogate marker.[10] In the UKPDS, changes in hemoglobin A_{1c} concentrations produced by drug treatment did not seem to correlate with treatment outcomes.

In study 33, an absolute reduction of 1% in the hemoglobin A_{1c} concentration compared with the group using diet alone was observed with the use of chlorpropamide, glibenclamide, or insulin over 10 years; yet, no significant reduction in the incidences of macrovascular outcomes occurred.[2] In study 34, all the drugs given—metformin, chlorpropamide, glibenclamide, and insulin—produced similar mean absolute differences in hemoglobin A_{1c} concentrations (about 0.6%) during the 10 years compared with diet alone, but only metformin produced significant reductions in clinically important macrovascular events.[3] Not only did metformin reduce the incidence of clinically important events compared with diet alone, it also reduced the incidence of some outcomes compared with other glucose-lowering drugs. This shows that the studies in question were large enough, and of sufficient duration, to demonstrate macrovascular benefits. Physicians and patients need to be aware of this and to consider that either metformin may be conferring benefit independent of, or in addition to, blood glucose reduction or that sulfonylureas and insulin may have an adverse effect on overall risk.[11] Further analysis of the study's findings may shed more light on this question.

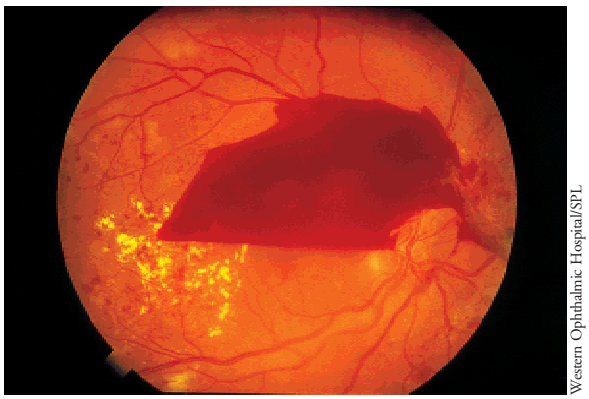
WHO INSERTS "SPIN" AND WHY?

In contrast to the "positive spin" about overall glucose control applied by many editorialists, the data show that the use of sulfonylureas and insulin led to only a small (3.2% absolute difference) reduction in an aggregate of clinical end points. In addition, the use of these drugs had no significant benefit on individual macrovascular end points in nonobese and obese patients with type 2 diabetes and no benefit at all in obese patients. However, the use of metformin, which provided a level of glucose control similar to that of sulfonylureas and insulin in obese type 2 diabetic patients, led to important (5%-10%) absolute reductions or delays in clinically important end points (death, strokes, and myocardial infarctions).

Why were the results from these studies presented with such a positive spin on tight blood glucose control when the results seem to show a benefit of the use of metformin over that of sulfonylureas and insulin? Are clinicians so reluctant to give up old beliefs? A similar spin was found with the Captopril Prevention Project, in which the use of captopril was compared with that of diuretics and β blockers for the treatment of hypertension.[12] Although, in general, no differences in cardiovascular outcomes occurred between the groups, patients taking diuretics and β blockers had a lower incidence of stroke (0.8% absolute difference) despite similar blood pressure reduction. If the reverse had been seen, the researchers possibly would have said something like, "these results demonstrate that angiotensin-converting enzyme inhibitors provide a unique benefit over other blood pressure-lowering agents." Instead, authors have tried to explain away the difference as being due to differences in baseline characteristics.

These cases illustrate the principle that interpretations of clinical trial results are often neither objective nor value-free. Rather, researchers, authors, and editors are highly susceptible to interpretive biases, including:

- "We've shown something here" bias—that is, the researchers' enthusiasm for a positive result. It took 20 years to collect and analyze the UKPDS data. To suggest that 2 of the 3 classes of drug used had little or no effect would have been a distinct anticlimax.
- "The result we've all been waiting for" bias—that is, the clinical and scientific communities' expectations. In the 1980s and early 1990s, it was widely believed that the strict control of blood glucose concentrations was the raison d'etre of the diabetologist and should be the principal objective of every well-behaved patient.
- "Just keep taking the tablets" bias—that is, the tendency of physicians to overestimate the benefits and underestimate the harms of drug treatment. All the primary reports of the UKPDS gave a relatively low emphasis to side effects (limited to hypoglycemia and weight gain, with little discussion of the effect these had on patients and no mention of other adverse events). Side effects were presented as events per year, although the purported benefits were presented over 10 years.



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Intensive glucose control may not reduce blindness in patients with diabetes

- "What can we tell the public?" bias—that is, the political need for regular, high-impact medical breakthroughs. Pressure from the press and patient support groups arguably drew staff from the British Diabetic Association, and perhaps even the trials' authors, into producing sound bites with a positive spin.
- "If enough people say it, it becomes true" bias—that is, the subconscious tendency of reviewers and editorial committees to "back a winner." The UKPDS results were published in high-quality, peer-reviewed journals and were probably seen before publication by at least a dozen independent experts in either diabetes or research methods. The writing—that the study was about to cause a sensation—was probably already on the wall, so it would have taken a brave and rebellious soul to be the first to jump off the bandwagon.

Looking back with the benefit of hindsight at how the UKPDS results were presented and received at the time, we think this is a good example of the hidden biases inherent in interpreting the results of randomized controlled trials. The relatively uncritical reception of the study by conference audiences, editorial committees, and the wider scientific community could be an example of mass groupthink—a well-described psychological phenomenon in which a group makes an overconfident and perhaps even irrational decision that it then defends fiercely against dissenting members, whose comments are subconsciously perceived as a threat to the group's cohesion.[13]

We put it to the editors of medical journals that they should, in the interests of minimizing interpretation bias, require investigators initially to present the results of clinical trials with a minimum of discussion so that physicians and patients can decide if the results are clinically important. In addition, we suggest that editors should continue to provide space for readers to enter a discourse about the meaning and clinical importance of those results, and indeed, they should actively stimulate discussion, perhaps by encouraging the publication of dissenting views. Furthermore, when new evidence challenges old beliefs, let it.

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References

1 University Group Diabetes Program. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. *Diabetes* 1970;19(suppl 2):747-830.
2 UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837-853 [published erratum appears in *Lancet* 1999;354:602].
3 UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;352:854-865 [published erratum appears in *Lancet* 1998;352:1557].
4 Ewart RM. The UKPDS: what was the question? [letter] *Lancet* 1999;353:1882.
5 Bailey CJ, Grant PJ. The UK Prospective Diabetes Study [letter]. *Lancet* 1998;352:1932; discussion 1934.
6 Gerstein HC. Intensive blood glucose control reduced type 2 diabetes mellitus-related end points. *ACP Journal Club* 1999 Jan/Feb:2-3.
7 Nathan DM. Some answers, more controversy, from UKPDS. United Kingdom Prospective Diabetes Study [comment]. *Lancet* 1998;352:832-833.
8 Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. *BMJ* 1995;310:452-454 [published erratum appears in *BMJ* 1995;310:1056].
9 Windeler J, Lange S. Events per person year–a dubious concept. *BMJ* 1995;310:454-456.
10 Greenhalgh T. How to read a paper: papers that report drug trials. *BMJ* 1997;315:480-483.
11 Kerner W. The UK Prospective Diabetes Study [letter]. *Lancet* 1998;352:1934.
12 Hansson L, Lindholm LH, Niskanen L, et al. Effects of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet* 1999;353:611-616.
13 Janis IL. *Groupthink: Psychological Studies of Policy Decisions and Fiascos.* Boston: Houghton Mifflin; 1982.

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